



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US97/03626 <b>(22) International Filing Date:</b> 7 March 1997 (07.03.97) <b>(30) Priority Data:</b> 60/013,138 8 March 1996 (08.03.96) US <b>(71) Applicant (for all designated States except US):</b> SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> JACKSON, Jeffrey, R. [US/US]; 134 Spruce Lane, Collegeville, PA 19426 (US). WINKLER, James, D. [US/US]; 701 Hartranft Avenue, Fort Washington, PA 19034 (US). <b>(74) Agents:</b> DINNER, Dara, L. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).		<b>(81) Designated States:</b> JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> USE OF CSAID™ COMPOUNDS AS INHIBITORS OF ANGIOGENESIS  <b>(57) Abstract</b>  The present invention is to the novel use of a cytokine inhibitor for the treatment of chronic diseases which are caused by excessive, undesired or inappropriate angiogenesis.		

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## Use of CSAID™ Compounds As Inhibitors of Angiogenesis

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### FIELD OF THE INVENTION

The present invention relates to the treatment of diseases, in a mammal, in which inappropriate, excessive or undesirable angiogenesis has occurred.

### 10 BACKGROUND OF THE INVENTION

Chronic diseases are often accompanied by profound angiogenesis, which can contribute to or maintain an inflammatory and/or proliferative state, or which leads to tissue destruction through the invasive proliferation of blood vessels. IL-1 $\beta$  and TNF $\alpha$  have been found to be potent inducers of angiogenesis *in vivo* and are commonly involved in the pathology of chronic inflammatory diseases (Folkman and Shing, J. Biol. Chem. 267:10931, 1992).

Angiogenesis is generally used to describe the development of new or replacement blood vessels, or neovascularisation. It is a necessary and physiologically normal process by which the vasculature is established in the embryo. Angiogenesis does not occur, in general, in the normal adult. Many diseases, however, are characterized by persistent and unregulated angiogenesis. For instance, in arthritis, new capillary blood vessels invade the joint and destroy cartilage (Colville-Nash and Scott, Ann. Rheum. Dis., 51, 919, 1992). In diabetes, new vessels invade the vitreous and blood, and cause blindness (and may occur in many different eye diseases) (Brooks et al., Cell, 79, 1157, 1994). The process of atherosclerosis has been linked to angiogenesis (Kahlon et al., Can. J. Cardiol. 8, 60, 1992). Tumor growth and metasis have been found to be angiogenesis-dependent (Folkman, Cancer Biol, 3, 65, 1992; Denekamp, Br. J. Rad. 66, 181, 1993; Fidler and Ellis, Cell, 79, 185, 1994).

The recognition of the involvement of angiogenesis in major diseases has been accompanied by research to identify and develop inhibitors of angiogenesis. These inhibitors are generally classified in response to discrete targets in the angiogenesis cascade, such as activation of endothelial cells by an angiogenic signal; synthesis and release of degradative enzymes; endothelial cell migration; proliferation of endothelial cells; and formation of capillary tubules. Therefore, angiogenesis occurs in many stages and attempts are underway to discover and develop compounds that work to block angiogenesis at these various stages.

There are publications that teach that inhibitors of angiogenesis, working by diverse mechanisms, are beneficial in diseases such as cancer and metastasis (O'Reilly et al., Cell, 79, 315, 1994; Ingber et al., Nature, 348, 555, 1990), ocular diseases (Friedlander et al., Science, 270, 1500, 1995), arthritis (Peacock et al., J. Exp. Med. 175, 1135, 1992; Peacock et al., Cell. Immun. 160, 178, 1995) and hemangioma (Taraboletti et al., J. Natl. Cancer Inst. 87, 293, 1995).

A need still exists, however, to find suitable small molecule inhibitors which will block angiogenesis in a mammal for treatment of these diseases which have an angiogenic component. The current application teaches the novel finding that CSAID™ compounds, i.e. compounds that block cytokine production, can block angiogenesis by removing the early cytokine signals for angiogenesis.

## SUMMARY OF THE INVENTION

The present invention is to the novel use of a cytokine inhibitor for the treatment of chronic inflammatory or proliferative or angiogenic diseases which are caused by excessive, inappropriate angiogenesis. The preferred compounds for use as cytokine inhibitors are those compounds of Formula (I) as noted herein. The preferred method of inhibition is the inhibition of the CSBP/p38/RK kinase pathway.

## BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A and 1B demonstrate the effects of Compound I, [1-Piperidine-4-(4-fluorophenyl)-5-(2-aminopyrimidin-4-yl)imidazole] on tissue dry weight and vascular index (mg carmine dye/ gm dry tissue) of Day 6 granulomas following treatment with compound I or medroxyprogesterone. Dosing began at the time granulomas were induced. Data is expressed as a percent of vehicle treated control animals +/- S.D. Control VI=5.4. control dry weight=0.28 gms. n=5. \* significant from control at p<0.05, calculated by Duncan's multiple range test.

Figures 2A-2D demonstrate the time course of granuloma development in murine air pouch angiogenesis model. Animals were orally dosed twice daily with either vehicle or 30 mg/kg compound I from Day 0 until removal of granuloma tissue at days 3, 5, 7, or 14. Granuloma size was determined by dry weight to control for possible differences in edema, A. Vascular index (mg carmine dye / gm dry tissue) was determined as described above, B. TNF- $\alpha$  levels within granuloma were determined by ELISA on tissue homogenates, C. IL-1 $\beta$  levels were determined by ELISA in the same tissue homogenates as C, D. Data are shown as

mean  $\pm$  S.D., n=5. \* significant from control at  $p < 0.05$ , \*\* significant from control at  $p < 0.01$ , calculated by Duncan's multiple range test.

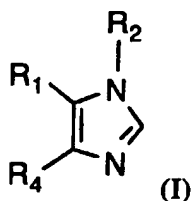
## DETAILED DESCRIPTION OF THE INVENTION

5 The present invention is to the novel use of a cytokine inhibitor, in particular that of cytokine CSBP/p38, for the treatment of chronic inflammatory diseases which are caused by excessive or inappropriate angiogenesis.

Compounds for use herein include the cytokine inhibitors as described in USSN 08/091,491, published as WO95/02575; WO96/21452; USSN 08/369,964; 10 USSN 08/473,396; USSN 08/659,102; USSN 08/764,003; WO96/40143; USSN 08/473,398; WO96/21654; WO93/14081; USSN 08/095,234; WO95/03297; USSN 08/481,671; PCT/US97/00619; PCT/US97/00614; PCT/US97/00500; PCT/US97/00529; USSN 60/013,357; USSN 60/013,358; USSN 60/013,359; WO93/14082; WO95/13067; and WO95/31451. Each of these references are 15 incorporated by reference herein in their entirety.

Preferred compounds for use as cytokine inhibitors are those compounds of Formula (I) as noted herein. Synthetic chemistry and methods of pharmaceutical formulations thereof are also contained within each noted patent application. A description of the assay for inhibition of the cytokine specific binding protein 20 (CSBP) is also found in WO95/07922, whose disclosure is incorporated by reference in its entirety.

A preferred group of compounds for use herein are those compounds of the formula:



25 wherein:

R<sub>1</sub> is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which heteroaryl ring is optionally substituted independently one to three times with Y, NHR<sub>a</sub>, optionally substituted C<sub>1-4</sub> alkyl, halogen, hydroxyl, optionally substituted C<sub>1-4</sub> alkoxy, optionally substituted C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkylsulfinyl, CH<sub>2</sub>OR<sub>12</sub>, amino, mono and di- C<sub>1-6</sub> alkyl substituted amino, or 30 N(R<sub>10</sub>)C(O)R<sub>b</sub>;

Y is O-R<sub>a</sub>;

- R<sub>4</sub> is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, -C(Z)NR<sub>7</sub>R<sub>17</sub>, -C(Z)OR<sub>16</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>COR<sub>12</sub>, -SR<sub>5</sub>, -SOR<sub>5</sub>, -OR<sub>12</sub>, halo-substituted-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkyl, -ZC(Z)R<sub>12</sub>, -NR<sub>10</sub>C(Z)R<sub>16</sub>, or  
 5 -(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>NR<sub>10</sub>R<sub>20</sub> and which, for other positions of substitution, is halogen, cyano, -C(Z)NR<sub>13</sub>R<sub>14</sub>, -C(Z)OR<sub>3</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>"COR<sub>3</sub>, -S(O)<sub>m</sub>R<sub>3</sub>, -OR<sub>3</sub>, halo-substituted-C<sub>1-4</sub> alkyl, -C<sub>1-4</sub> alkyl, -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>"NR<sub>10</sub>C(Z)R<sub>3</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>'R<sub>8</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>'NR<sub>7</sub>R<sub>17</sub>, -ZC(Z)R<sub>3</sub> or -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>"NR<sub>13</sub>R<sub>14</sub>;
- 10 v is 0, or an integer having a value of 1 or 2;  
 m is 0, or the integer 1 or 2;  
 m' is an integer having a value of 1 or 2;  
 m" is 0, or an integer having a value of 1 to 5;
- 15 R<sub>2</sub> is C<sub>1-10</sub> alkyl N<sub>3</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>'OR<sub>9</sub>, heterocyclyl, heterocyclylC<sub>1-10</sub> alkyl, C<sub>1-10</sub>alkyl, halo-substituted C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub> cycloalkenyl C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub>alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NHS(O)<sub>2</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NO<sub>2</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CN, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>'SO<sub>2</sub>R<sub>18</sub>,  
 20 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>'NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)R<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)R<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)OR<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)NR<sub>11</sub>OR<sub>9</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>10</sub>C(Z)R<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>10</sub>C(Z)NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(OR<sub>6</sub>)C(Z)NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(OR<sub>6</sub>)C(Z)R<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(=NOR<sub>6</sub>)R<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>10</sub>C(=NR<sub>19</sub>)NR<sub>13</sub>R<sub>14</sub>,  
 25 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>10</sub>C(Z)NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>10</sub>C(Z)OR<sub>10</sub>, 5-(R<sub>18</sub>)-1,2,4-oxadiazol-3-yl or 4-(R<sub>12</sub>)-5-(R<sub>18</sub>R<sub>19</sub>)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;
- n is an integer having a value of 1 to 10;
- 30 n' is 0, or an integer having a value of 1 to 10;  
 Z is oxygen or sulfur;
- R<sub>a</sub> is C<sub>1-6</sub>alkyl, aryl, arylC<sub>1-6</sub>alkyl, heterocyclic, heterocyclylC<sub>1-6</sub> alkyl, heteroaryl, or heteroarylC<sub>1-6</sub>alkyl, wherein each of these moieties may be optionally substituted;
- 35 R<sub>b</sub> is hydrogen, C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub>alkyl, heterocyclyl, or heterocyclylC<sub>1-4</sub> alkyl;
- R<sub>3</sub> is heterocyclyl, heterocyclylC<sub>1-10</sub> alkyl or R<sub>8</sub>;

- R<sub>5</sub> is hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>7</sub>R<sub>17</sub>, excluding the moieties -SR<sub>5</sub> being -SNR<sub>7</sub>R<sub>17</sub> and -SOR<sub>5</sub> being -SOH;
- R<sub>6</sub> is hydrogen, a pharmaceutically acceptable cation, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclic, aroyl, or C<sub>1-10</sub> alkanoyl;
- 5 R<sub>7</sub> and R<sub>17</sub> is each independently selected from hydrogen or C<sub>1-4</sub> alkyl or R<sub>7</sub> and R<sub>17</sub> together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>15</sub>;
- 10 R<sub>8</sub> is C<sub>1-10</sub> alkyl, halo-substituted C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>5-7</sub> cycloalkenyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NHS(O)<sub>2</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>13</sub>R<sub>14</sub>; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;
- 15 R<sub>9</sub> is hydrogen, -C(Z)R<sub>11</sub> or optionally substituted C<sub>1-10</sub> alkyl, S(O)<sub>2</sub>R<sub>18</sub>, optionally substituted aryl or optionally substituted aryl-C<sub>1-4</sub> alkyl;
- R<sub>10</sub> and R<sub>20</sub> is each independently selected from hydrogen or C<sub>1-4</sub> alkyl;
- R<sub>11</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, heterocyclyl, heterocyclyl C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl or heteroarylC<sub>1-10</sub> alkyl;
- R<sub>12</sub> is hydrogen or R<sub>16</sub>;
- 20 R<sub>13</sub> and R<sub>14</sub> is each independently selected from hydrogen or optionally substituted C<sub>1-4</sub> alkyl, optionally substituted aryl or optionally substituted aryl-C<sub>1-4</sub> alkyl, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>;
- 25 R<sub>15</sub> is R<sub>10</sub> or C(Z)-C<sub>1-4</sub> alkyl;
- R<sub>16</sub> is C<sub>1-4</sub> alkyl, halo-substituted-C<sub>1-4</sub> alkyl, or C<sub>3-7</sub> cycloalkyl;
- R<sub>18</sub> is C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C<sub>1-10</sub>alkyl, heteroaryl or heteroarylalkyl;
- R<sub>19</sub> is hydrogen, cyano, C<sub>1-4</sub> alkyl, C<sub>3-7</sub> cycloalkyl or aryl;
- 30 or a pharmaceutically acceptable salt thereof.
- Suitably R<sub>1</sub> is a substituted 4-pyridyl or 4-pyrimindyl. More suitably R<sub>1</sub> is substituted by alkoxy, alkylthio, amino, methylamino, NHR<sub>a</sub>, or Y. A preferred ring placement of the R<sub>1</sub> substituent on the 4-pyridyl derivative is the 2-position, such as 2-methoxy-4-pyridyl. A preferred ring placement on the 4-pyrimidinyl ring is also at the 2-
- 35 position, such as in 2-methoxy-pyrimidinyl.

When the substituent is Y, and R<sub>a</sub> is aryl, it is preferably phenyl or naphthyl. When R<sub>a</sub> is aryl alkyl, it is preferably benzyl or naphthylmethyl. When R<sub>a</sub> is heterocyclic or heterocyclic alkyl moiety, the heterocyclic portion is preferably pyrrolindinyl, piperidine, morpholino, tetrahydropyran, tetrahydrothiopyran, tetrahydrothiopyran-sulfinyl,

- 5 tetrahydrothio-pyransulfonyl, pyrrolindinyl, indole, or piperonyl. It is noted that the heterocyclic rings herein may contain unsaturation, such as in a tryptamine ring.

- The aryl, heterocyclic and heteroaryl rings may be optionally substituted one or more times independently with halogen; C<sub>1-4</sub> alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted alkyl, such as CF<sub>3</sub>; hydroxy; hydroxy substituted C<sub>1-4</sub> alkyl; C<sub>1-4</sub> alkoxy, such as methoxy or ethoxy; S(O)<sub>m</sub>alkyl and S(O)<sub>m</sub> aryl (wherein m is 10 0, 1, or 2); C(O)OR<sub>11</sub>, such as C(O)C<sub>1-4</sub> alkyl or C(O)OH moieties; C(O)R<sub>11</sub>; -OC(O)R<sub>c</sub>; O-(CH<sub>2</sub>)<sub>s</sub>-O-, such as in a ketal or dioxyalkylene bridge; amino; mono- and di-C<sub>1-6</sub> alkylsubstituted amino; -N(R<sub>10</sub>)C(O)R<sub>b</sub>; -C(O)NR<sub>10</sub>R<sub>20</sub>; cyano, nitro, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional 15 heteroatom selected from oxygen, sulfur or NR<sub>15</sub>; aryl, such as phenyl; an optionally substituted arylalkyl, such as benzyl or phenethyl; aryloxy, such as phenoxy; or arylalkyloxy such as benzyloxy. Wherein R<sub>c</sub> is optionally substituted C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub>alkyl, heterocyclyl, or heterocyclylC<sub>1-4</sub> alkyl moieties.

- 20 Preferably, the R<sub>a</sub> groups include benzyl, halosubstituted benzyl, naphthylmethyl, phenyl, halosubstituted phenyl, aminocarbonylphenyl, alkylphenyl, cyanophenyl, alkylthiophenyl, hydroxyphenyl, alkoxyphenyl, morpholinopropyl, piperonyl, piperidin-4-yl, alkyl substituted piperidine, such as 1-methyl piperidine, or 2,2,6,6-tetramethylpiperidin-4-yl.

- 25 Preferably, when the substituent is NHR<sub>a</sub> then R<sub>a</sub> is aryl, arylalkyl, halosubstituted arylalkyl, halosubstituted aryl, heterocyclic alkyl, hydroxy alkyl, alkyl-1-piperidine-carboxylate, heterocyclic, alkyl substituted heterocyclic, halosubstituted heterocyclic, or aryl substituted heterocyclic. More specifically R<sub>a</sub> is benzyl, halosubstituted benzyl, naphthylmethyl, phenyl, halosubstituted phenyl, morpholinopropyl, 30 2-hydroxy ethyl, ethyl-1-piperidinecarboxylate, piperonyl, piperidin-4-yl, alkyl substituted piperidine, chlorotryptamine, and tetrathiohydropyran.

- Preferably, when the substituent is a substituted C<sub>1-4</sub> alkoxy or C<sub>1-4</sub> alkylthio, the alkyl chain is substituted by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy, such as hydroxyethoxy; C<sub>1-10</sub> alkoxy, such as a methoxymethoxy, S(O)<sub>m</sub> alkyl, 35 wherein m is 0, 1 or 2; amino, mono & di-substituted amino, such as in the NR<sub>7</sub>R<sub>17</sub> group, i.e. tert-butylaminoethoxy; or where the R<sub>7</sub>R<sub>17</sub> may together with the nitrogen to which



they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C<sub>1-10</sub> alkyl, cycloalkyl, or cycloalkyl alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; or halosubstituted C<sub>1-10</sub> alkyl, such as CF<sub>3</sub>. Preferably the R<sub>1</sub> substituents are

5 tertbutylaminoethoxy, or hydroxyethoxy.

Suitably, R<sub>4</sub> is an optionally substituted phenyl. Preferably the phenyl is substituted one or more times independently by halogen, -SR<sub>5</sub>, -S(O)R<sub>5</sub>, -OR<sub>12</sub>, halo-substituted-C<sub>1-4</sub> alkyl, or C<sub>1-4</sub> alkyl.

Suitably, R<sub>2</sub> is selected from C<sub>1-10</sub> alkyl, optionally substituted heterocyclyl, 10 optionally substituted heterocyclylC<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NS(O)<sub>2</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>18</sub>, arylC<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>13</sub>R<sub>14</sub>, optionally substituted C<sub>3-7</sub>cycloalkyl, or optionally substituted C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl. Preferably R<sub>2</sub> is morpholino propyl, piperidine, N-methylpiperidine, N-benzylpiperidine, 2,2,6,6-tetramethylpiperidine, 4-aminopiperidine, 4-amino-2,2,6,6-tetramethyl piperidine, 15 4-hydroxycyclohexyl, 4-methyl-4-hydroxy cyclohexyl, 4-pyrrolinindyl-cyclohexyl, 4-methyl-4-aminocyclohexyl, 4-methyl-4-acetamidocyclohexyl, 4-keto cyclohexyl, 4-oxiranyl, or 4-hydroxy-4-(1-propynyl)cyclohexyl.

Preferably R<sub>2</sub> is an optionally substituted heterocyclyl ring, and optionally substituted heterocyclylC<sub>1-10</sub> alkyl, an optionally substituted C<sub>1-10</sub> alkyl, an optionally 20 substituted C<sub>3-7</sub>cycloalkyl, an optionally substituted C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)OR<sub>11</sub> group, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NHS(O)<sub>2</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>18</sub>, an optionally substituted aryl; an optionally substituted arylC<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)R<sub>11</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(=NOR<sub>6</sub>)R<sub>11</sub> group.

More preferably R<sub>2</sub> is an optionally substituted heterocyclyl ring, and optionally 25 substituted heterocyclylC<sub>1-10</sub> alkyl, optionally substituted aryl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>13</sub>R<sub>14</sub>, or (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)OR<sub>11</sub> group.

When R<sub>2</sub> is an optionally substituted heterocyclyl, the ring is preferably a morpholino, pyrrolidinyl, or a piperidinyl group. When the ring is optionally substituted, the substituents may be directly attached to the free nitrogen, such as in the piperidinyl 30 group or pyrrole ring, or on the ring itself. Preferably the ring is a piperidine or pyrrole, more preferably piperidine. The heterocyclyl ring may be optionally substituted one to four times independently by halogen; C<sub>1-4</sub> alkyl; aryl, such as phenyl; aryl alkyl, such as benzyl - wherein the aryl or aryl alkyl moieties themselves may be optionally substituted (as in the definition section below); C(O)OR<sub>11</sub>, such as the C(O)C<sub>1-4</sub> alkyl or C(O)OH 35 moieties; C(O)H; C(O)C<sub>1-4</sub> alkyl, hydroxy substituted C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, S(O)<sub>m</sub>C<sub>1-</sub>

4 alkyl (wherein m is 0, 1, or 2), NR<sub>10</sub>R<sub>20</sub> (wherein R<sub>10</sub> and R<sub>20</sub> are independently hydrogen or C<sub>1-4</sub>alkyl).

Preferably if the ring is a piperidine, the ring is attached to the imidazole at the 4-position, and the substituents are directly on the available nitrogen, i.e. a

5 1-Formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine, 1-ethoxycarbonyl-4-piperidine. If the ring is substituted by an alkyl group and the ring is attached in the 4-position, it is preferably substituted in the 2- or 6- position or both, such as 2,2,6,6-tetramethyl-4-piperidine. Similarly, if the ring is a pyrrole, the ring is attached to the imidazole at the 3-position, and the substituents are all directly on the available nitrogen.

10 When R<sub>2</sub> is an optionally substituted heterocyclyl C<sub>1-10</sub> alkyl group, the ring is preferably a morpholino, pyrrolidinyl, or a piperidinyl group. Preferably this alkyl moiety is from 1 to 4, more preferably 3 or 4, and most preferably 3, such as in a propyl group. Preferred heterocyclic alkyl groups include but are not limited to, morpholino ethyl, morpholino propyl, pyrrolidinyl propyl, and piperidinyl propyl moieties. The heterocyclic  
15 ring herein is also optionally substituted in a similar manner to that indicated above for the direct attachment of the heterocyclyl.

When R<sub>2</sub> is an optionally substituted C<sub>3-7</sub>cycloalkyl, or an optionally substituted C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl, the cycloalkyl group is preferably a C<sub>4</sub> or C<sub>6</sub> ring, most preferably a C<sub>6</sub> ring, which ring is optionally substituted. The cycloalkyl  
20 ring may be optionally substituted one to three times independently by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; C<sub>1-10</sub> alkoxy, such as methoxy or ethoxy; S(O)<sub>m</sub> alkyl, wherein m is 0, 1, or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; S(O)<sub>m</sub> aryl; cyano, nitro, amino, mono & di-substituted amino, such as in the NR<sub>7</sub>R<sub>17</sub> group, wherein R<sub>7</sub> and R<sub>17</sub> are as defined in Formula (I), or where  
25 the R<sub>7</sub>R<sub>17</sub> may cyclize together with the nitrogen to which they are attached to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from oxygen, sulfur or NR<sub>15</sub> (and R<sub>15</sub> is as defined for Formula (I)); N(R<sub>10</sub>)C(O)X<sub>1</sub> (wherein R<sub>10</sub> is as defined for Formula (I)), and X<sub>1</sub> is C<sub>1-4</sub> alkyl, aryl or arylC<sub>1-4</sub>alkyl); N(R<sub>10</sub>)C(O) aryl; C<sub>1-10</sub> alkyl, such as methyl, ethyl, propyl,  
30 isopropyl, or t-butyl; optionally substituted alkyl wherein the substituents are halogen, (such as CF<sub>3</sub>), hydroxy, nitro, cyano, amino, mono & di-substituted amino, such as in the NR<sub>7</sub>R<sub>17</sub> group, S(O)<sub>m</sub> alkyl and S(O)<sub>m</sub> aryl, wherein m is 0, 1 or 2; optionally substituted alkylene, such as ethylene or propylene; optionally substituted alkyne, such as ethyne; C(O)OR<sub>11</sub> (wherein R<sub>11</sub> is as defined in Formula (I)), such as the free acid  
35 or methyl ester derivative; the group R<sub>e</sub>; -C(O)H; =O; =N-OR<sub>11</sub>; -N(H)-OH (or substituted alkyl or aryl derivatives thereof on the nitrogen or the oxime moiety);

-N(OR<sub>d</sub>)-C(O)-R<sub>6</sub>'; an optionally substituted aryl, such as phenyl; an optionally substituted arylC<sub>1-4</sub>alkyl, such as benzyl or phenethyl; an optionally substituted heterocycle or heterocyclic C<sub>1-4</sub>alkyl, and further these aryl, arylalkyl, heterocyclic, and heterocyclic alkyl moieties are optionally substituted one to two times by halogen, hydroxy, C<sub>1-10</sub> alkoxy, S(O)<sub>m</sub> alkyl, cyano, nitro, amino, mono & di-substituted amino, such as in the NR<sub>7</sub>R<sub>17</sub> group, an alkyl, halosubstituted alkyl.

Suitably R<sub>d</sub> is hydrogen, a pharmaceutically acceptable cation, aroyl or a C<sub>1-10</sub> alkanoyl group.

Suitably R<sub>e</sub> is a 1,3-dioxyalkylene group of the formula -O-(CH<sub>2</sub>)<sub>s</sub>-O-, wherein s is 1 to 3, preferably s is 2 yielding a 1,3-dioxyethylene moiety, or ketal functionality.

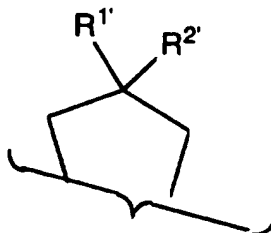
Suitably R<sub>6</sub>' is NR<sub>19</sub>'R<sub>20</sub>'; alkyl 1-6; halosubstituted alkyl 1-6; hydroxy substituted alkyl 1-6; alkenyl 2-6; aryl or heteroaryl optionally substituted by halogen, alkyl 1-6, halosubstituted alkyl 1-6, hydroxyl, or alkoxy 1-6.

Suitably R<sub>19</sub>' is H or alkyl 1-6.

Suitably R<sub>20</sub>' is H, alkyl 1-6, aryl, benzyl, heteroaryl, alkyl substituted by halogen or hydroxyl, or phenyl substituted by a member selected from the group consisting of halo, cyano, alkyl 1-12, alkoxy 1-6, halosubstituted alkyl 1-6, alkylthio, alkylsulphonyl, or alkylsulfinyl; or R<sub>19</sub>' and R<sub>20</sub>' may together with the nitrogen to which they are attached form a ring having 5 to 7 members, which members may be optionally replaced by a heteroatom selected from oxygen, sulfur or nitrogen. The ring may be saturated or contain more than one unsaturated bond. Preferably R<sub>6</sub>' is NR<sub>19</sub>'R<sub>20</sub>' and R<sub>19</sub>' and R<sub>20</sub>' are preferably hydrogen.

When the R<sub>2</sub> cycloalkyl moiety is substituted by NR<sub>7</sub>R<sub>17</sub> group, or NR<sub>7</sub>R<sub>17</sub> C<sub>1-10</sub> alkyl group, and the R<sub>7</sub> and R<sub>17</sub> are as defined in Formula (I), the substituent is preferably an amino, amino alkyl, or an optionally substituted pyrrolidinyl moiety.

A preferred ring placement on the cycloalkyl moiety is the 4-position, such as in a C<sub>6</sub> ring. When the cycloalkyl ring is di-substituted it is preferably di-substituted at the 4 position, such as in:



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wherein R<sup>1'</sup> and R<sup>2'</sup> are independently the optional substituents indicated above for R<sub>2</sub>.

Preferably, R<sup>1'</sup> and R<sup>2'</sup> are hydrogen, hydroxy, alkyl, substituted alkyl, optionally substituted alkyne, aryl, arylalkyl, NR<sub>7</sub>R<sub>17</sub>, and N(R<sub>10</sub>)C(O)R<sub>11</sub>. Suitably, alkyl is C<sub>1-4</sub> alkyl, such as methyl, ethyl, or isopropyl; NR<sub>7</sub>R<sub>17</sub> and NR<sub>7</sub>R<sub>17</sub> alkyl, such as amino, methylamino, aminomethyl, aminoethyl; substituted alkyl such as in cyanomethyl, cyanoethyl, nitroethyl, pyrrolidinyl; aryl such as in phenyl; arylalkyl, such as in benzyl; optionally substituted alkyne, such as ethyne or propynyl; or together R<sup>1'</sup> and R<sup>2'</sup> are a keto functionality.

Preferably R<sub>2</sub> is an optionally substituted heterocyclic, heterocyclic C<sub>1-4</sub> alkyl, a cycloalkyl or a cycloalkyl alkyl. More preferably R<sub>2</sub> is an optionally substituted C<sub>4</sub> or C<sub>6</sub> cycloalkyl, cyclopropyl methyl, morpholinyl butyl, morpholinyl propyl, morpholinyl ethyl, cyclohexyl substituted by methyl, phenyl, benzyl, amino, acetamide, aminomethyl, aminoethyl, cyanomethyl, cyanoethyl, hydroxy, nitroethyl, pyrrolidinyl, ethynyl, 1-propynyl, =O, O-(CH<sub>2</sub>)<sub>2</sub>O-, =NOR<sub>11</sub>, wherein R<sub>11</sub> is hydrogen, alkyl or aryl, NHOH, or N(OH)-C(O)-NH<sub>2</sub>; or R<sub>2</sub> is morpholinyl propyl, aminopropyl, piperidinyl, N-benzyl-4-piperidinyl, N-methyl-4-piperidinyl, 2,2,6,6-tetramethylpiperidinyl, substituted piperidine, such as 1-Formyl-4-piperidine, or a 1-ethoxycarbonyl-4-piperidine.

In all instances herein where there is an alkenyl or alkynyl moiety as a substituent group, the unsaturated linkage, i.e., the vinylenic or acetylenic linkage is preferably not directly attached to the nitrogen, oxygen or sulfur moieties, for instance in OR<sub>3</sub>, or for certain R<sub>2</sub> moieties.

As used herein, "optionally substituted", unless specifically defined, shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C<sub>1-10</sub>alkyl; C<sub>1-10</sub> alkoxy, such as methoxy or ethoxy; S(O)<sub>m</sub> alkyl, wherein m is 0, 1 or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR<sub>7</sub>R<sub>17</sub> group; or where the R<sub>7</sub>R<sub>17</sub> may together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C<sub>1-10</sub> alkyl, cycloalkyl, or cycloalkyl alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; halosubstituted C<sub>1-10</sub> alkyl, such as CF<sub>3</sub>; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, wherein these aryl moieties may also be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C<sub>1-10</sub> alkoxy; S(O)<sub>m</sub> alkyl; amino, mono & di-substituted amino, such as in the NR<sub>7</sub>R<sub>17</sub> group; alkyl, or CF<sub>3</sub>.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid,

hydrobromic acid, sulfuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be  
5 formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The following terms, as used herein, refer to:

- 10       • "halo" or "halogens", include the halogens: chloro, fluoro, bromo and iodo.  
      • "C<sub>1-10</sub>alkyl" or "alkyl" - both straight and branched chain radicals of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- 15       • The term "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.  
      • The term "cycloalkenyl" is used herein to mean cyclic radicals, preferably of 5 to 8 carbons, which have at least one bond including but not limited to cyclopentenyl, cyclohexenyl, and the like.
- 20       • The term "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;
- 25       • "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, or
- 30 benzimidazole.
- "heterocyclic" (on its own or in any combination, such as "heterocyclalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydro pyran, or
- 35 imidazolidine.

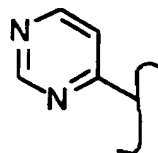
• The term "alkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C<sub>1-4</sub> alkyl as defined above attached to an aryl, heteroaryl or heterocyclic moiety as also defined herein unless otherwise indicated.

• "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized S(O)<sub>2</sub> moiety.

• "aroyl" - a C(O)Ar, wherein Ar is a phenyl, naphthyl, or aryl alkyl derivative such as defined above, such groups include but are not limited to benzyl and phenethyl.

• "alkanoyl" - a C(O)C<sub>1-10</sub> alkyl wherein the alkyl is as defined above.

For the purposes herein the "core" 4-pyrimidinyl moiety for R<sub>1</sub> or R<sub>2</sub> is referred to as the formula:



The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

As noted previously, methods of making these compounds can be found in their respective patent applications as noted above.

Compounds of Formula (I) are capable of inhibiting proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF.

The compounds of Formula (I) may also be used topically in the treatment or prophylaxis of disease states exacerbated by excessive or inappropriate angiogenesis.

The compounds of Formula (I) are administered in an amount sufficient to inhibit cytokine, in particular IL-1, IL-6, IL-8 or TNF, production such that it is regulated down to normal levels, or in some cases to subnormal levels, so as to ameliorate or prevent the disease state. Abnormal levels of IL-1, IL-6, IL-8 or TNF, for instance in the context of the present invention, constitute: (i) levels of free (not cell bound) IL-1, IL-6, IL-8 or TNF greater than or equal to 1 picogram per ml; (ii) any cell associated IL-1, IL-6, IL-8 or TNF; or (iii) the presence of IL-1, IL-6, IL-8 or TNF mRNA above basal levels in cells or tissues in which IL-1, IL-6, IL-8 or TNF, respectively, is produced.

As used herein, the term "inhibiting the production of IL-1 (IL-6, IL-8 or TNF)" refers to:

a) a decrease of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels by inhibition of the *in vivo* release of the cytokine by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the genomic level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels;

c) a down regulation, by inhibition of the direct synthesis of the cytokine (IL-1, IL-6, IL-8 or TNF) as a postranslational event; or

5 d) a down regulation, at the translational level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels.

As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells, however, also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes and B-lymphocytes.

10 Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) and Tumor Necrosis Factor beta (TNF- $\beta$ ).

As used herein, the term "cytokine interfering" or "cytokine suppressive amount" refers to an effective amount of a compound of Formula (I) which will cause a decrease in the *in vivo* levels of the cytokine to normal or sub-normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

A new member of the MAP kinase family, alternatively termed CSBP, p38, or RK, has been identified independently by several laboratories recently. Activation of this novel protein kinase via dual phosphorylation has been observed in different cell systems upon stimulation by a wide spectrum of stimuli, such as physicochemical stress and treatment with lipopolysaccharide or proinflammatory cytokines such as interleukin-1 and tumor necrosis factor. The cytokine biosynthesis inhibitors of the present invention, compounds of Formula (I) have been determined to be potent and selective inhibitors of CSBP/p38/RK kinase activity. These inhibitors are of aid in determining the signaling pathways involvement in inflammatory responses. In particular, for the first time a definitive signal transduction pathway can be prescribed to the action of lipopolysaccharide in cytokine production in macrophages. In addition to those diseases already noted, treatment of stroke, neurotrauma, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, diabetes

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and pancreatic  $\beta$  cells, multiple sclerosis, muscle degeneration, eczema, psoriasis, sunburn, and conjunctivitis are also included.

The cytokine inhibitors were subsequently tested in a number of animal models for anti-inflammatory activity. Model systems were chosen that were relatively  
5 insensitive to cyclooxygenase inhibitors in order to reveal the unique activities of cytokine suppressive agents. The inhibitors exhibited significant activity in many such in vivo studies. Most notable are its effectiveness in the collagen-induced arthritis model and inhibition of TNF production in the endotoxic shock model. In the latter study, the reduction in plasma level of TNF correlated with survival and protection from endotoxic  
10 shock related mortality. Also of great importance are the compounds effectiveness in inhibiting bone resorption in a rat fetal long bone organ culture system. Griswold et al., (1988) *Arthritis Rheum.* 31:1406-1412; Badger, et al., (1989) *Circ. Shock* 27, 51-61; Votta et al., (1994) *in vitro. Bone* 15, 533-538; Lee et al., (1993). *B Ann. N. Y. Acad. Sci.* 696, 149-170.

15 In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent.

20 Compounds of Formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of Formula (I) may be administered in conventional dosage forms prepared by combining a compound of Formula (I) with  
25 standard pharmaceutical carriers according to conventional procedures. The compounds of Formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically  
30 acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the Formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid.  
35 Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup,



peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

5 A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

10 Compounds of Formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of Formula (I) externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and  
15 intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from  
20 0.001% to 10% w/w, for instance from 1% to 2% by weight of the Formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the Formulation.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally  
25 containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid  
30 formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such  
35 as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The

Formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

5        Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably include a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and  
10        sterilized by autoclaving or maintaining at 98-100 C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution  
15        include glycerol, diluted alcohol and propylene glycol.

Compounds of formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by  
20        conventional techniques. Compounds of Formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

For all methods of use disclosed herein for the compounds of Formula (I), the daily  
25        oral dosage regimen will preferably be from about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to 30 mg/kg, more preferably from about 0.5 mg to 15mg. The daily parenteral dosage regimen will be from about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from about 0.5 mg to 15mg/kg. The daily topical dosage regimen will preferably be from 0.1  
30        mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being  
35        treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be

appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

5           Chronic diseases which have an inappropriate angiogenic component are various ocular neovascularizations, such as diabetic retinopathy and macular degeneration.

Other chronic diseases which have an excessive or increased proliferation of vasculature are tumor growth and metastasis, atherosclerosis, and certain arthritic  
10       conditions. Therefore cytokine inhibitors will be of utility in the blocking of the angiogenic component of these disease states.

The term "excessive or increased proliferation of vasculature inappropriate angiogenesis" as used herein includes, but is not limited to, diseases which are characterized by hemangiomas and ocular diseases.

15           The term "inappropriate angiogenesis" as used herein includes, but is not limited to, diseases which are characterized by vesicle proliferation with accompanying tissue proliferation, such as occurs in cancer, metastasis, arthritis and atherosclerosis.

Described below a model of inflammatory angiogenesis is used to show that  
20       cytokine inhibition will stop the tissue destruction of excessive or inappropriate proliferation of blood vessels. Based on these observations, a cytokine inhibitor, 1-Piperidine-4-(4-fluorophenyl)-5-(2-aminopyrimidin-4-yl)imidazole - Compound I was tested for its ability to inhibit angiogenesis in an *in vivo* animal model of inflammatory angiogenesis.

25           The murine airpouch granuloma model of chronic inflammation (Kimura et al., 1985, J. Pharmacobio-Dyn., 8:393-400; Colville-Nash et al., 1995, J. Pharm. and Exp. Ther., 274:1463-1472) whose disclosure is incorporated herein by reference in its entirety, is characterized by inflammatory cell influx, fibrous tissue proliferation and intense angiogenesis. It is representative of inflammatory angiogenesis and  
30       demonstrates that the angiogenic component can be pharmacologically modulated independently of granuloma growth and size. In addition, angiogenesis can be accurately quantitated by a vascular casting method.

The effect of the compound on vascular density (and dry weight) was measured for 6 days after induction of the granuloma. (Figures 1a and 1b) This  
35       time point has been determined to be at or near the peak of angiogenesis. Compound I demonstrated a significant and dose dependent decrease in the vascular

index with a maximum reduction of 44% at 50 mg.kg, bid, i.p. As a positive control medroxyprogesterone, an angiostatic steroid (Gross et al., 1981, Proc. Natl. Acad. Sci. USA, 78:1176-1180) - whose disclosure is hereby incorporated by reference in its entirety, was utilized. This control demonstrated a maximum reduction of 50% in  
5 this model. Neither Compound I nor medroxyprogesterone had an effect on granuloma size as measured by dry weight.

Angiogenesis in the granuloma was microscopically evaluated. The vasculature of day 6 granulomas from both untreated and compound I treated mice was examined. The profound angiogenesis in the granuloma is demonstrated by the  
10 extensive vascular network in the control tissue. There was a striking reduction in the vasculature of the treated tissue. In fact, there was almost no fine capillaries visible, only a few larger vessels.

The effect of the compound on angiogenesis was also evaluated at several time points, to determine if its effects would be different at the various stages of  
15 inflammatory and angiogenic progression. Compound I was given orally, at an intermediate dose of 30 mg/kg twice a day starting on day 0, and granulomas were evaluated on days 3, 5, 7, and 14. Granuloma size remained fairly constant and was unaffected by the compound (Fig. 2). The VI of the control group rose gradually from day 3 to 14, whereas the VI of the treated group remained level. At day 3, the  
20 compound did not cause a significant reduction in VI compared to control, however, at days 5, 7, and 14, the VI was lowered significantly. Thus the compound did not affect the initial burst of angiogenesis, but did prevent the increase in angiogenesis which occurs following day 3.

Inflammatory cytokines such as IL-1 $\beta$  and TNF- $\alpha$  have been implicated in  
25 the pathogenesis of angiogenesis in chronic inflammation, and the compound has been demonstrated to inhibit the synthesis of these cytokines. The levels of these cytokines over the course to granuloma development were measured to determine if the modulation of their expression by the compound correlated with angiogenesis. Cytokine levels were measured by ELISA using homogenates of granuloma tissue.  
30 TNF- $\alpha$  levels rose sharply, peaking at day 7 and dropping back down to moderate levels by day 14 (Fig. 2). Compound I greatly reduced TNF- $\alpha$  levels at day 7. IL- $\beta$  levels were also high in control granulomas, peaking at day 7, and as with TNF- $\alpha$ , the compound effectively blocked the increased IL-1 $\beta$  expression. Thus, the ability of the compound to block the sharp rise in TNF- $\alpha$  and IL-1 $\beta$  between days 5 and 7  
35 correlated well with the ability of the compound to prevent the increase in vascular index that occurs over the same time points.

## Methods

### Murine air pouch granuloma model:

Day -1, mice are anesthetized using Aerrane (isoflurane) gas (5%), after  
5 which 3mls of air is injected into the dorsal subcutaneous tissue using a 27g needle.  
Mice are allowed to recover.

Day 0, mice are again anesthetized using Aerrane, once anesthetized 0.5ml of  
Freunds complete adjuvant with 0.1% v/v croton oil is injected into the air pouch  
formed on Day -1. The animals also begin their dosing regime (number of days  
10 dependent upon study) with the animals typically receiving compound in 0.2ml N,N,  
Dimethyl Acetoacetamide(DMA)(Sigma, St. Louis, Mo.)/Cremephor El (Sigma, St.  
Louis, Mo.)/ saline (10/10/80) or other appropriate vehicle. The animals are allowed  
to recover and all subsequent dosing is performed on the animals in the absence of  
anesthetics.

15 Days 1-5, animals are dosed according to schedule.

On Day 6 the animals are again anesthetized using Aerrane after which a  
vascular cast is made (Kimura et al., 1986, J.Pharmacobio-Dyn., 9:442-446), this  
involves a 1ml tail vein i.v. injection of a Carmine Red(10%)(Sigma, St. Louis,  
Mo.)/ gelatin (5%)(Sigma, St. Louis, Mo.) solution. The animals are then sacrificed  
20 by lethal dose of anesthesia and chilled at 4 C for 2 hours prior to the removal of the  
granuloma tissue.

When the granuloma is removed it is weighed and then dried for 3 days at  
45 C and reweighed. The dried tissue is then digested in 0.9ml of a 0.05M phosphate  
buffer pH 7.0 containing 12 U /ml<sup>-1</sup> papain (Sigma, St. Louis, Mo.) and 0.33g / L<sup>-1</sup>  
25 N-acetyl-L-Cysteine (Sigma, St. Louis, Mo.) at 57 C for 3 days. After 3 days  
digestion the carmine red is solubilized by the addition of 0.1ml 5mM NaOH.  
Samples are centrifuged and then filtered using 0.2um acrodiscs. The carmine  
content is then determined against a carmine red standard curve (0.5 to 2 mg/ml)  
generated in extracted tissue from non carmine treated animals and read at 490nm.  
30 Sample and standard values are determined using DeltaSoft Elisa analysis software  
(Biometallics Inc., Princeton, NJ). The carmine content is then used to determine  
the vascular indexes for the various treatments, vascular index being the mg carmine  
dye/gm dry tissue.

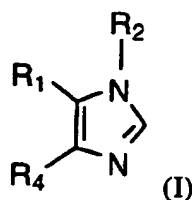
Tissue extracts were made by homogenizing granulomas in 0.5ml 5mM  
35 KH<sub>2</sub>PO<sub>4</sub> / 0.1gm wet tissue. IL-1 $\beta$  levels were determined using a Cytoscreen  
Immunoassay Kit (catalog # KMC 0012) from BioSource International, Camarillo,

CA. TNF- $\alpha$  levels were determined using the following assay: plates were coated with hamster anti-murine TNF- $\alpha$  antibody (Genzyme, Cambridge, MA), for 2 hours at 37°C, washed and blocked with a casein-BSA solution (5gram/L for each) for 1 hour at 37°C, the samples were added and incubated at 4°C overnight. Plates were  
5 washed, and the secondary antibody, Rabbit Anti-mouse TNF- $\alpha$  (Genzyme), was added for 2 hours at 37°C, the plates were washed, and the tertiary antibody Goat Anti-rabbit peroxidase conjugate (BioSource International, Camarillo, CA) was added for 2 hours at 37°C. The plates were then washed, and substrate OPD (Sigma) was added for 20 minutes at room temperature. The reaction was  
10 terminated with 25ul 0.1M NaF per well, the O.D. read at 460nm. Sample values for both ELISAs are calculated using DeltaSoft ELISA analysis software (Biometalics Inc., Princeton, NJ).

The above description fully discloses the invention including preferred  
15 embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the  
Examples herein are to be construed as merely illustrative and not a limitation of the  
20 scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed is:

1. A method of treating a chronic disease in a mammal in need thereof, which disease is characterized by excessive, undesired or inappropriate angiogenesis, with  
5 an effective amount of a compound which inhibits the production, transcription or translation of a cytokine.
2. The method according to Claim 1 wherein the cytokine is inhibited by inhibition of the kinase CSBP/p38/RK.
- 10 3. The method according to Claim 1 wherein the cytokine is IL-1 $\beta$ .
4. The method according to Claim 1 wherein the cytokine is TNF- $\alpha$ .
- 15 5. The method according to Claims 1 to 4 wherein the disease is diabetic retinopathy and other ocular neovascularizations.
6. The method according to Claims 1 to 4 wherein the disease is tumor growth and metastasis.
- 20 7. The method according to Claims 1 to 4 wherein the disease is atherosclerosis.
8. The method according to Claims 1 to 4 wherein the disease is arthritis.
- 25 9. The method according to Claim 1 wherein the compound is of the formula:



wherein:

- 30 R<sub>1</sub> is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl ring, which ring is optionally substituted independently one to three times with Y, NHR<sub>a</sub>, optionally substituted C<sub>1-4</sub> alkyl, halogen, hydroxyl, optionally

substituted C<sub>1-4</sub> alkoxy, optionally substituted C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkylsulfinyl, CH<sub>2</sub>OR<sub>12</sub>, amino, mono and di- C<sub>1-6</sub> alkyl substituted amino, or N(R<sub>10</sub>)C(O)R<sub>b</sub>; Y is OR<sub>a</sub>;

- R<sub>4</sub> is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, -C(Z)NR<sub>7</sub>R<sub>17</sub>, -C(Z)OR<sub>16</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>COR<sub>12</sub>, -SR<sub>5</sub>, -SOR<sub>5</sub>, -OR<sub>12</sub>, halo-substituted-C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkyl, -ZC(Z)R<sub>12</sub>, -NR<sub>10</sub>C(Z)R<sub>16</sub>, or -(CR<sub>10</sub>R<sub>20</sub>)<sub>v</sub>NR<sub>10</sub>R<sub>20</sub> and which, for other positions of substitution, is halogen, cyano, -C(Z)NR<sub>13</sub>R<sub>14</sub>, -C(Z)OR<sub>3</sub>, -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>"COR<sub>3</sub>, -S(O)<sub>m</sub>R<sub>3</sub>, -OR<sub>3</sub>, halo-substituted-C<sub>1-4</sub> alkyl, -C<sub>1-4</sub> alkyl, -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>"NR<sub>10</sub>C(Z)R<sub>3</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>'R<sub>8</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>'NR<sub>7</sub>R<sub>17</sub>, -ZC(Z)R<sub>3</sub> or -(CR<sub>10</sub>R<sub>20</sub>)<sub>m</sub>"NR<sub>13</sub>R<sub>14</sub>;
- v is 0, or an integer having a value of 1 or 2;
- m is 0, or the integer 1 or 2;
- m' is an integer having a value of 1 or 2,
- m" is 0, or an integer having a value of 1 to 5;
- R<sub>2</sub> is -(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>'OR<sub>9</sub>, heterocyclyl, heterocyclylC<sub>1-10</sub> alkyl, C<sub>1-10</sub>alkyl, halo-substituted C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-10</sub> alkyl, C<sub>5-7</sub> cycloalkenyl, C<sub>5-7</sub> cycloalkenylC<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub>alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NHS(O)<sub>2</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NO<sub>2</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CN, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>SO<sub>2</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>'NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)R<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)R<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)OR<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(Z)NR<sub>11</sub>OR<sub>9</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>10</sub>C(Z)R<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>10</sub>C(Z)NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(OR<sub>6</sub>)C(Z)NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>N(OR<sub>6</sub>)C(Z)R<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>C(=NOR<sub>6</sub>)R<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>10</sub>C(=NR<sub>19</sub>)NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OC(Z)NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>10</sub>C(Z)NR<sub>13</sub>R<sub>14</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>10</sub>C(Z)OR<sub>10</sub>, 5-(R<sub>18</sub>)-1,2,4-oxadiazol-3-yl or 4-(R<sub>12</sub>)-5-(R<sub>18</sub>R<sub>19</sub>)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;
- n is an integer having a value of 1 to 10;
- n' is 0, or an integer having a value of 1 to 10;
- Z is oxygen or sulfur;
- R<sub>a</sub> is C<sub>1-6</sub>alkyl, aryl, arylC<sub>1-6</sub>alkyl, heterocyclic, heterocyclylC<sub>1-6</sub> alkyl, heteroaryl, or heteroarylC<sub>1-6</sub>alkyl, wherein each of these moieties may be optionally substituted;



- R<sub>b</sub> is hydrogen, C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub>alkyl, heterocyclyl, or heterocyclylC<sub>1-4</sub> alkyl;
- R<sub>3</sub> is heterocyclyl, heterocyclylC<sub>1-10</sub> alkyl or R<sub>8</sub>;
- R<sub>5</sub> is hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-4</sub> alkynyl or NR<sub>7</sub>R<sub>17</sub>, excluding the  
5 moieties -SR<sub>5</sub> being -SNR<sub>7</sub>R<sub>17</sub> and -SOR<sub>5</sub> being -SOH;
- R<sub>6</sub> is hydrogen, a pharmaceutically acceptable cation, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, aryl, arylC<sub>1-4</sub> alkyl, heteroaryl, heteroarylC<sub>1-4</sub> alkyl, heterocyclic, aroyl, or C<sub>1-10</sub> alkanoyl;
- R<sub>7</sub> and R<sub>17</sub> is each independently selected from hydrogen or C<sub>1-4</sub> alkyl or R<sub>7</sub> and R<sub>17</sub> together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7  
10 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>15</sub>;
- R<sub>8</sub> is C<sub>1-10</sub> alkyl, halo-substituted C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>5-7</sub> cycloalkenyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl, heteroarylC<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>OR<sub>11</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NHS(O)<sub>2</sub>R<sub>18</sub>,  
15 (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>13</sub>R<sub>14</sub>; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;
- R<sub>9</sub> is hydrogen, -C(Z)R<sub>11</sub> or optionally substituted C<sub>1-10</sub> alkyl, S(O)<sub>2</sub>R<sub>18</sub>, optionally substituted aryl or optionally substituted aryl-C<sub>1-4</sub> alkyl;
- R<sub>10</sub> and R<sub>20</sub> is each independently selected from hydrogen or C<sub>1-4</sub> alkyl;
- 20 R<sub>11</sub> is hydrogen, C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, heterocyclyl, heterocyclyl C<sub>1-10</sub>alkyl, aryl, arylC<sub>1-10</sub> alkyl, heteroaryl or heteroarylC<sub>1-10</sub> alkyl;
- R<sub>12</sub> is hydrogen or R<sub>16</sub>;
- R<sub>13</sub> and R<sub>14</sub> is each independently selected from hydrogen or optionally substituted C<sub>1-4</sub> alkyl, optionally substituted aryl or optionally substituted aryl-C<sub>1-4</sub> alkyl, or together  
25 with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR<sub>9</sub>;
- R<sub>15</sub> is R<sub>10</sub> or C(Z)-C<sub>1-4</sub> alkyl;
- R<sub>16</sub> is C<sub>1-4</sub> alkyl, halo-substituted-C<sub>1-4</sub> alkyl, or C<sub>3-7</sub> cycloalkyl;
- 30 R<sub>18</sub> is C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C<sub>1-10</sub>alkyl, heteroaryl or heteroarylalkyl;
- R<sub>19</sub> is hydrogen, cyano, C<sub>1-4</sub> alkyl, C<sub>3-7</sub> cycloalkyl or aryl;  
or a pharmaceutically acceptable salt thereof.
- 35 10. The compound according to Claim 9 wherein R<sub>1</sub> is a substituted 4-pyridyl or 4-pyrimindyl.

11. The compound according to Claim 9 wherein  $R_a$  is aryl, arylalkyl, halosubstituted arylalkyl, halosubstituted aryl, heterocyclic alkyl, hydroxy alkyl, alkyl-1-piperidine-carboxylate, heterocyclic, alkyl substituted heterocyclic, halosubstituted heterocyclic, or aryl substituted heterocyclic.
- 5 12. The compound according to Claim 11 wherein  $R_a$  is benzyl, halosubstituted benzyl, naphthylmethyl, phenyl, halosubstituted phenyl, morpholinopropyl, 2-hydroxy ethyl, ethyl-1-piperidinecarboxylate, piperonyl, piperidin-4-yl, alkyl substituted piperidine, chlorotryptamine, and tetrathiohydropyranlyl.
- 10 13. The compound according to Claim 9 wherein  $R_4$  is an optionally substituted phenyl.
- 15 14. The compound according to Claim 9 wherein  $R_2$  is selected from optionally substituted heterocyclcyl, optionally substituted heterocyclcylC<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NS(O)<sub>2</sub>R<sub>18</sub>, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>S(O)<sub>m</sub>R<sub>18</sub>, arylC<sub>1-10</sub> alkyl, (CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>13</sub>R<sub>14</sub>, optionally substituted C<sub>3-7</sub>cycloalkyl, or optionally substituted C<sub>3-7</sub>cycloalkyl C<sub>1-10</sub> alkyl.
- 20 15. The compound according to Claim 14 wherein  $R_2$  is morpholino propyl, piperidine, N-methylpiperidine, N-benzylpiperidine, 2,2,6,6-tetramethylpiperidine, 4-aminopiperidine, 4-amino-2,2,6,6-tetramethyl piperidine, 4-hydroxycyclohexyl, 4-methyl-4-hydroxy cyclohexyl, 4-pyrrolinindyl-cyclohexyl, 4-methyl-4-aminocyclohexyl, 4-methyl-4-acetamidocyclohexyl, 4-keto cyclohexyl, 4-oxiranyl,
- 25 or 4-hydroxy-4-(1-propynyl)cyclohexyl.

FIGURE 1A

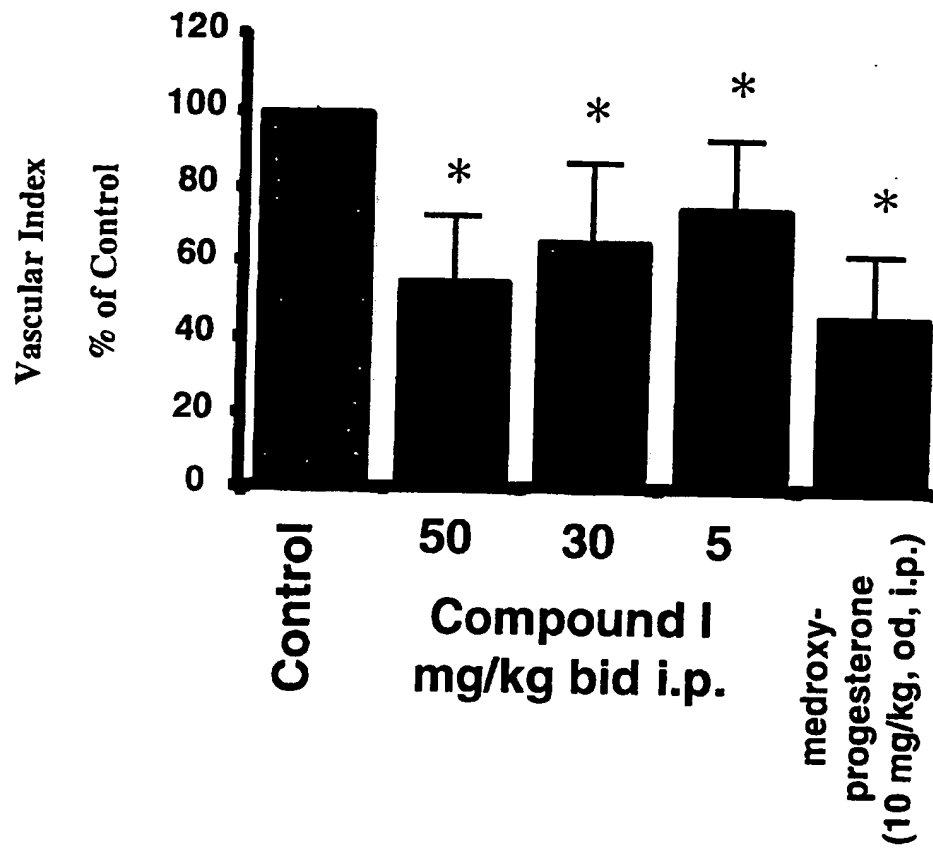


FIGURE 1B

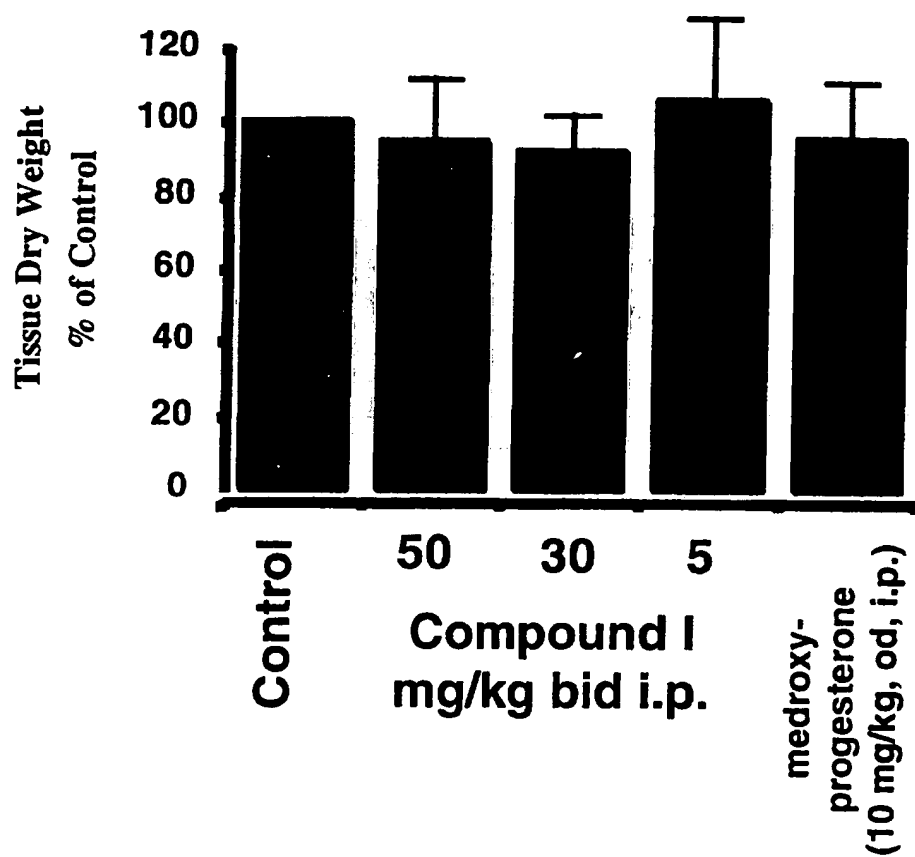


FIGURE 2A

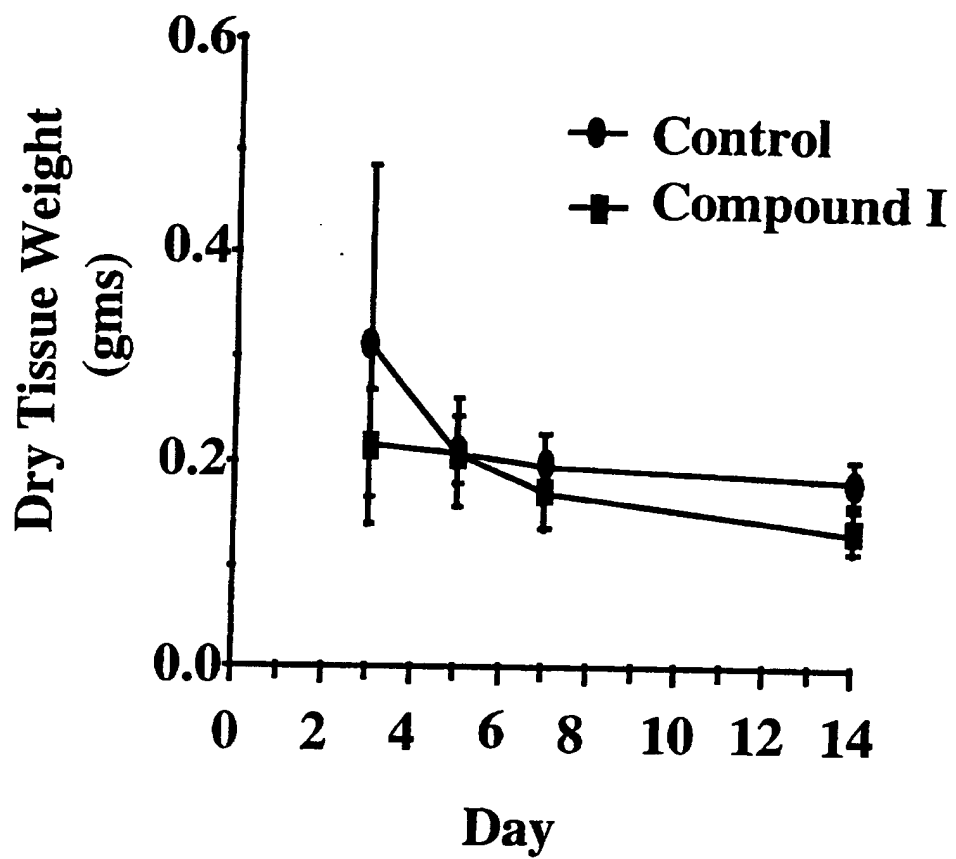


FIGURE 2B

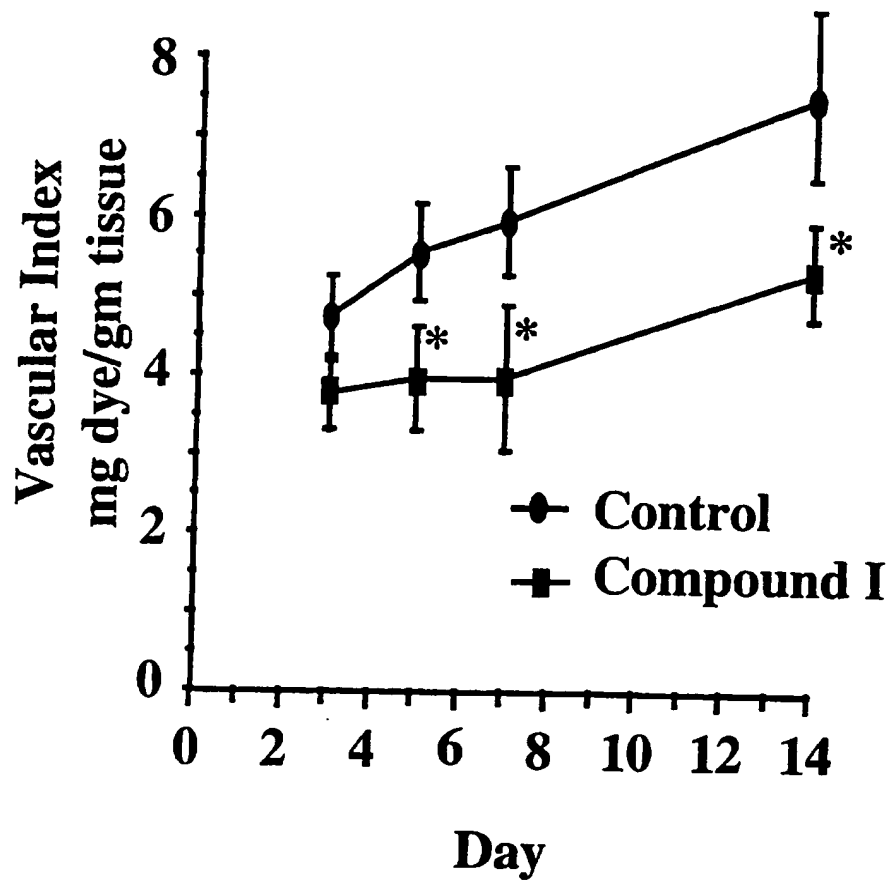


FIGURE 2C

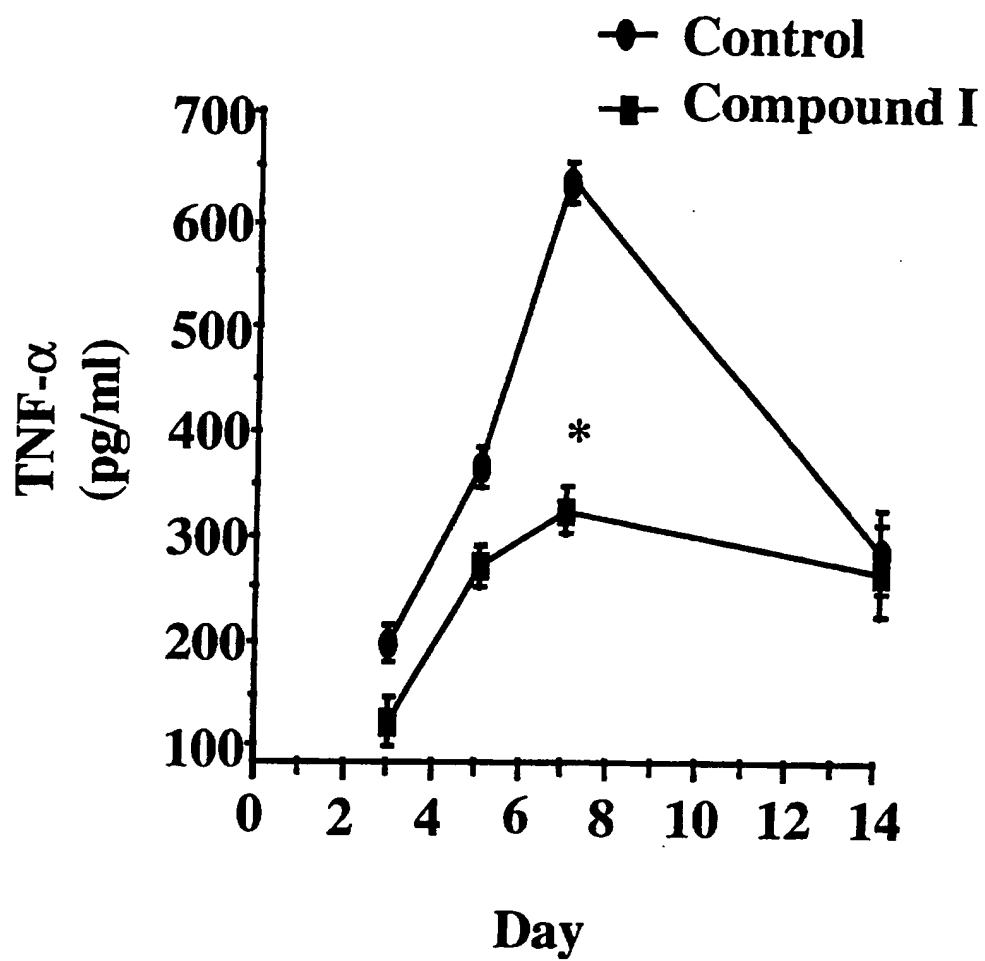
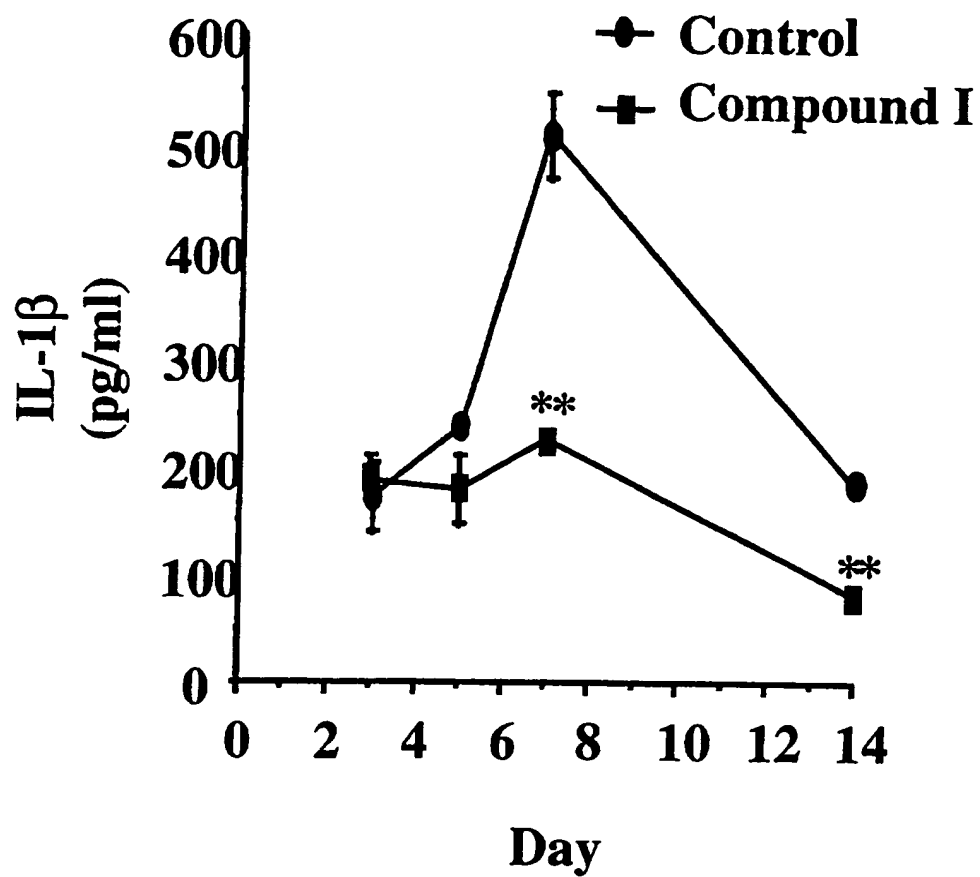


FIGURE 2D





## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/03626

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : A61K 31/44, 31/47, 31/415, 31/505

US CL : 514/256, 259, 307, 314, 341, 394, 397

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/256, 259, 307, 314, 341, 394, 397

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 5,525,724 A (HUNDS) 11 June 1996, column 2, lines 45-50.	9-14
A, P	US 5,525,604 A (LEE et al) 11 June 1996, column 10, lines 5-55.	9-14

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 04 JUNE 1997	Date of mailing of the international search report 27 JUN 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer YOGENDRA N. GUPTA Telephone No. (703) 308-1235

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/03626

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 1-8  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
Claims 1-8 are drawn to a method of use without identifying the compound to be used in the claimed composition. The claims as written are non-limiting and are thus, indefinite and unsearchable.
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.